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A PROCESS FOR OPTICAL RESOLUTION OF MANDELIC ACID DERIVATIVES

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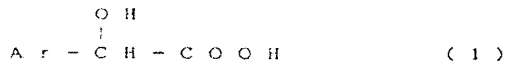
Specification

1. Title of the Invention

A process for optical resolution of mandelic acid derivatives.

2. Sole Patent Claim

A process for optical resolution of mandelic acid or mandelic acid derivatives represented by the following formula (1), characterised by subjecting to crystallisation step in a form of diastereomeric salt of amino acid hydrazide.



(1)

In the formula, Ar denotes a phenyl group or substituted phenyl group.

3. Detailed Description of the Invention

Sphere of Application in Industry

This invention is a process for the optical resolution of mandelic acid and mandelic acid derivatives (hereinafter, collectively called "mandelic acid derivatives"). Optically active mandelic acid derivatives are anticipated to be used for example as a synthetic intermediate of pharmaceuticals and the like.

Technology of the Prior Art

Processes and the like using recrystallisation of complex with amino acid and a salt of optically acitive amine such as alkaloid or the like (cf. for example USP 4,224,239) have been known as optical resolution methods of mandelic acid, however, there is no process which can be applied

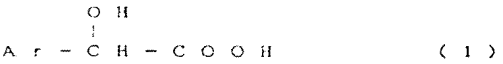
widely to the resolution of mandelic acid derivatives, and the development of a novel resolution agent is desired.

Problems to be Overcome by this Invention

This invention is to carry out optical resolution of mandelic acid derivatives which has been difficult to resolve by the technology of prior art. Moreover, the said process, by using inexpensive raw material, is also superior from the cost aspects compared to the technology of prior art.

Means to Overcome these Problems

These inventors carried out assiduous investigations in order to solve the aforesaid problems, and as a result discovered that the optical resolution could be carried out by forming a salt of mandelic acid derivative represented by the following formula (1)



(1)

(in the formula, Ar denotes a phenyl group or substituted phenyl group)

with an amino acid hydrazide in a solvent and crystallising one of the diastereomers. This invention was completed on the basis of this discovery. Mandelic acid derivatives can be obtained in 50-90%ee optical purity by acidifying the obtained crystals in water.

The amino acid hydrazide used in this invention is not limited in particular, but hydrazides of neutral amino acids such as leucine, valine, alanine, phenylalanine, thyrosin and the like are preferred, and these can be synthesised inexpensively by adding hydrazide to an alcohol solution of an amino acid ester. Moreover, the amount of amino acid hydrazide used is preferably 0.5-1.0 equivalent based on the mandelic acid derivative.

As a solvent used for optical resolution, water and hydrous or anhydrous alcohols, in particular alcohols such as methanol, ethanol and the like are preferred, however, ethers such as dioxane and the like can be used.

Moreover, the mandelic acid derivative having 50-90%ee of optical purity obtained in accordance with this process can be subjected to recrystallisation, and thereby its optical purity can be further increased. Moreover, when extraction solvent of mandelic acid derivative is concentrated, racemic compound crystals precipitate, and therefore crystals of high optical purity can be recovered from the mother liquor.

In accordance with this invention, mandelic acid derivatives which were difficult to optically resolve by the technology of prior art can be isolated with high optical purity. For example, 2-(3,4-O-isopropylidene dioxyphenyl)-2-hydroxy acetic acid can be obtained in a high yield with optical purity of 99%ee or more.

Examples

Below, this invention will be explained in detail by reference to Examples.

Example 1

Isopropanol 500 ml solution of L-leucine hydrazide 6.5 g (45 mmol) was warmed to 60°C, and thereto was added racemic body of 2-(3,4-O-isopropylidene dioxyphenyl)-2-hydroxy acetic acid (hereinafter abbreviated to IPMA) 10 g (45 mmol). Stirring was carried out at 60°C for 30 minutes, and thereafter, the temperature was gradually lowered, and stirring was further carried out at 20°C for two hours. The thereby precipitated salt comprised (R)-IPMA of optical purity 86%ee. The crystals were recovered by filtration, and the recovered crystals were suspended in water and adjusted to pH2 by adding sulfuric acid while stirring. Thereto was added ethyl acetate and extraction was carried out, thereafter the organic layer was concentrated to 45 ml, and precipitation was carried out with stirring at 20°C. The crystals were eliminated by filtration, the mother liquor was concentrated, and as a result, (R)-IPMA of optical purity 99%ee or more was obtained in an amount of 3.2 g (14.3 mmol). The yield from IPMA of racemic body was 64%.

Example 2

A solution of L-leucine hydrazide 7.9 g (54.4 mmol) dissolved in methanol 120 ml was warmed to 60°C, and thereto was added racemic body of IPMA 12.2 g (54.4 mmol). Stirring was carried out at 60°C for 30 minutes, thereafter, the temperature was gradually lowered, and stirring was further carried out at 5°C for two hours. The thereby precipitated salt comprised (R)-IPMA of optical purity 90%ee. The crystals were recovered by filtration, and the recovered crystals were suspended in water and adjusted to pH2 by adding sulfuric acid while stirring. Thereto was added ethyl acetate and extraction was carried out, thereafter the organic layer was concentrated to 50 ml, and precipitation was carried out with stirring at 20°C. The crystals were eliminated by filtration, the mother liquor was concentrated, and as a result, (R)-IPMA of optical purity 99%ee or more was obtained in an amount of 4.3 g (19.2 mmol). The yield from IPMA of racemic body was 70%.

Example 3

A solution of L-leucine hydrazide 0.65 g (4.5 mmol) dissolved in dioxane 50 ml was warmed to

40°C, and thereto was added racemic body of IPMA 1.0 g (4.5 mmol). Stirring was carried out at 40°C for 30 minutes, thereafter, the temperature was gradually lowered, and stirring was further carried out at 20°C for two hours. The crystals were recovered by filtration, and the recovered crystals were suspended in water and adjusted to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 0.52 g (2.3 mmol) of (R)-IPMA of optical purity 65%ee was obtained.

Example 4

A methanol solution 5 ml of L-leucine hydrazide 0.98 g (6.7 mmol) was warmed to 40°C, and thereto was added racemic body of IPMA 3.0 g (13.4 mmol). The mixture was stirred at 40°C for 30 minutes, thereafter the temperature was gradually lowered, and stirring was further carried out at 5°C for two hours. The crystals were filtered, the filtrated crystals were suspended in water and adjusted the pH to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 1.6 g (7.1 mmol) of (R)-IPMA of optical purity 80%ee was obtained.

Example 5

A methanol solution 100 ml of L-tyrosine hydrazide 7.8 g (40 mmol) was warmed to 60°C, and thereto was added racemic body of IPMA 9.0 g (40 mmol). The mixture was stirred at 60°C for 30 minutes, thereafter, the temperature was gradually lowered, and stirring was further carried out at 5°C for two hours. The crystals were recvoered by filtration, the recvoered crystals were suspended in water and the pH was adjusted to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 3.6 g (16 mmol) of (S)-IPMA of optical purity 85%ee was obtained.

Example 6

To a methanol solution 3 ml of L-valine hydrazide 0.29 g (2.2 mmol) was added racemic body of IPMA 0.5 g (2.2 mmol). Thereto was added isopropanol 5 ml, crystallisation caused, the crystals stirred at 5°C for further two hours were recovered by filtration, and the recovered crystals were suspended in water and the pH was adjusted to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 0.18 g (0.8 mmol) of (R)-IPMA of optical purity 80%ee was obtained.

Example 7

A solution of L-leucine hydrazide 12 g (82 mmol) dissolved in methanol 150 ml was warmed to 40°C, and thereto was added racemic body of mandelic acid 15.2 g (100 mmol). Stirring was carried out at 40°C for 30 minutes, thereafter, the temperature was gradually lowered, and stirring

was further carried out at 5°C for two hours. The crystals were recovered by filtration, and the recovered crystals were suspended in water and adjusted to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 5.4 g (36 mmol) of (R)-mandelic acid of optical purity 85%ee was obtained.

Example 8

To a solution of L-leucine hydrazide 2.4 g (17 mmol) dissolved in methanol 20 ml was added racemic body of 4-chloromandelic acid 4.1 g (20 mmol). Stirring was carried out at 5°C for two hours, and precipitation was carried out. The crystals were recovered by filtration, and the recovered crystals were suspended in water and adjusted to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 2.1 g (10 mmol) of (R)-4-chloromandelic acid of optical purity 70%ee was obtained.

Example 9

To a solution of L-leucine hydrazide 2.4 g (17 mmol) dissolved in methanol 10 ml was added racemic body of 4-hydroxy mandelic acid 3.7 g (20 mmol). Ethanol 10 ml was added to this liquid, and the mixture was stirred at 5°C for further two hours to cause precipitation. The crystals were recovered by filtration, and the recovered crystals were suspended in water and the pH was adjusted to pH2 by adding sulfuric acid while stirring. The crystals were filtered again and dried, and thereby 1.6 g (8.6 mmol) of (R)-4-hydroxy mandelic acid of optical purity 65%ee was obtained.

Advantages Afforded by this Invention

As is clear from the above, in accordance with this invention, the optical resolution on mandelic acid derivatives can be readily carried out, and therefore this invention is extremely useful.

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⑬公開　平成1年(1989)9月4日

審査請求　未請求　請求項の数 1　（全4頁）

⑤4発明の名称　マンデル酸誘導体の光学分割方法

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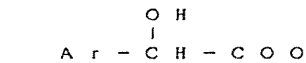
明　細　書

1．発明の名称

マンデル酸誘導体の光学分割方法

2．特許請求範囲

アミノ酸ヒドラジドとのジアステレオマー塩の形で晶析工程に付することを特徴とする下記一般式（1）に示されるマンデル酸またはマンデル酸誘導体の光学分割方法。



（1）

上記式中、Arはフェニル基または置換基を有するフェニル基を表す。

3．発明の詳細な説明

［産業上の利用分野］

本発明は、マンデル酸およびマンデル酸誘導体（以下、併せて単に「マンデル酸誘導体」と呼ぶ）の光学分割方法である。光学活性なマンデル酸誘導体は、例えば医薬品等の合成中間体としての利用が期待される。

［従来の技術］

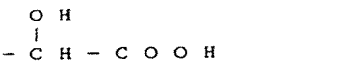
マンデル酸の光学分割方法としてはアルカロイド等の光学活性アミンとの塩やアミノ酸とのコンプレックスの再結晶を利用する方法等が知られているが（例えばUSP 4，224，239参照）、広くマンデル酸誘導体の分割に応用可能な方法はなく、新たな分割剤の開発が望まれる。

［発明が解決しようとする課題］

従来の技術では分割が困難とされるマンデル酸誘導体の光学分割をおこなおうというものである。また、安価な原料を用いることにより従来の技術に比べコスト面でも優れたものとする。

［課題を解決するための手段］

前記課題を解決すべく、発明者らは鋭意検討した結果、下記一般式（１）



（１）

（上記式中、Ａｒはフェニル基または置換基を有するフェニル基を表す。）

で示されるマンデル酸誘導体をアミノ酸のヒドラジドと溶媒中で塩を形成させることにより、一方のジアステレオマーを晶析させ、光学分割を行うことができることを見出しこの発見に基づいて本発明を完成するに到った。　得られた結晶を水中で酸性にすることにより５０－９０％ｅｅの光学純度でマンデル酸誘導体が得られる。

本方法に用いられるアミノ酸のヒドラジドとしては特に制限はないが、好ましくはロイシン、バリン、アラニン、フェニルアラニン、チロシン等の中性アミノ酸のヒドラジドがよく、これらはアミノ酸エステルのアルコール溶液にヒドラジンを加えることで安価に合成できる。　また、用いるアミノ酸ヒドラジドの量はマンデル酸誘導体の０．５－１．０当量がよい。

光学分割に用いる溶媒としては、水、及び含水もしくは無水アルコール類、特にメタノール、エタノール等のアルコールが望ましいが、ジオキサンのようなエーテル類も使用可能である。

また、本方法により得られた５０－９０％ｅｅの光学純度をもつマンデル酸誘導体は、さらに再結晶によって光学純度を上げることができる。また、マンデル酸誘導体の抽出溶媒を濃縮すればラセミ化合物結晶が晶析するので、母液中から高い光学純度の結晶を回収することができる。

本発明方法を用いると、従来の方法で光学分割が困難であったマンデル酸誘導体を高い光学純度で単離することができる。　例えば、２－（３、４－Ｏ－イソプロピリデンジオキシフェニル）－２－ヒドロキシ酢酸は９９％ｅｅ以上の光学純度でかつ高収率で得られる。

［実施例］

以下、実施例により本発明を具体的に説明する。

実施例　１

Ｌ－ロイシンヒドラジド６．５ｇ（４５ｍｍｏｌ）をイソプロパノール５００ｍｌに溶解した液を６０℃にし、ラセミ体の　２－（３、４－Ｏ－イソプロピリデンジオキシフェニル）－２－ヒドロキシ酢酸（以下、ＩＰＭＡと略す）を１０ｇ（４５ｍｍｏｌ）を加えた。　６０℃で３０分間撹拌した後、温度を徐々に下げ、２０℃でさらに２時間撹拌した。　ここで析出した塩は光学純度８６％ｅｅの（Ｒ）－ＩＰＭＡよりなるものであった。　結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　これに酢酸エチルを加え抽出した後、有機層を４５ｍｌに濃縮し２０℃で撹拌し晶析を行った。　結晶を濾過し取り除き母液を濃縮したところ９９％ｅｅ以上の（Ｒ）－ＩＰＭＡを３．２ｇ（１４．３ｍｍｏｌ）得た。ラセミ体のＩＰＭＡからの収率は６４％であった。

実施例　２

Ｌ－ロイシンヒドラジド７．９ｇ（５４．４ｍｍｏｌ）をメタノール１２０ｍｌに溶解した液を６０℃にし、ラセミ体のＩＰＭＡを１２．２ｇ（５４．４ｍｍｏｌ）を加えた。　６０℃で３０分間撹拌した後、温度を徐々に下げ、５℃でさらに２時間撹拌した。　ここで析出した塩は光学純度９０％ｅｅの（Ｒ）－ＩＰＭＡよりなるものであった。　結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　これに酢酸エチルを加え抽出した後、有機層を５０ｍｌに濃縮し２０℃で撹拌し晶析を行った。　結晶を濾過し取り除き母液を濃縮したところ９９％ｅｅ以上の（Ｒ）－ＩＰＭＡを４．３ｇ（１９．２ｍｍｏｌ）得た。ラセミ体のＩＰＭＡからの収率は７０％であった。

実施例　3

Ｌ－ロイシンヒドラジド　0．６５ｇ（４．５ｍｍｏｌ）をジオキサン５０ｍｌに溶解した液を４０℃にし、ラセミ体のＩＰＭＡを１．０ｇ（４．５ｍｍｏｌ）を加えた。　４０℃で３０分間撹拌した後、温度を徐々に下げ、２０℃でさらに２時間撹拌した。　結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。再び結晶を濾過して乾燥し、光学純度６５％ｅｅの（Ｒ）－ＩＰＭＡを０．５２ｇ（２．３ｍｍｏｌ）得た。

実施例　4

Ｌ－ロイシンヒドラジド０．９８ｇ（６．７ｍｍｏｌ）をメタノール５ｍｌに溶解した液を４０℃にし、ラセミ体のＩＰＭＡを３．０ｇ（１３．４ｍｍｏｌ）を加えた。　４０℃で３０分間撹拌した後、温度を徐々に下げ、５℃でさらに２時間撹拌した。　結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再析し、５℃でさらに２時間撹拌した結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再び結晶を濾過して乾燥し、光学純度８０％ｅｅの（Ｒ）－ＩＰＭＡを０．１８ｇ（０．８ｍｍｏｌ）得た。

実施例　7

Ｌ－ロイシンヒドラジド１２ｇ（８２ｍｍｏｌ）をメタノール１５０ｍｌに溶解した液を４０℃にし、ラセミ体のマンデル酸１５．２ｇ（１００ｍｍｏｌ）を加えた。　４０℃で３０分間撹拌した後、温度を徐々に下げ、５℃でさらに２時間撹拌した。結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再び結晶を濾過して乾燥し、光学純度８５％ｅｅの（Ｒ）－マンデル酸５．４ｇ（３６ｍｍｏｌ）得た。

実施例　8

Ｌ－ロイシンヒドラジド２．４ｇ（１７ｍｍｏｌ）をメタノール２０ｍｌに溶解した液にし、ラセミ体のＩＰＭＡを１．０ｇ（４．５ｍｍｏｌ）を加えた。　４０℃で３０分間撹拌した後、温度を徐々に下げ、２０℃でさらに２時間撹拌した。　結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。再び結晶を濾過して乾燥し、光学純度８０％ｅｅの（Ｒ）－ＩＰＭＡを１．６ｇ（７．１ｍｍｏｌ）得た。

実施例　5

Ｌ－チロシンヒドラジド７．８ｇ（４０ｍｍｏｌ）をメタノール１００ｍｌに溶解した液を６０℃にし、ラセミ体のＩＰＭＡ９．０ｇ（４０ｍｍｏｌ）を加えた。　６０℃で３０分間撹拌した後、温度を徐々に下げ、５℃でさらに２時間撹拌した。結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再び結晶を濾過して乾燥し、光学純度８５％ｅｅの（Ｓ）－ＩＰＭＡを３．６ｇ（１６ｍｍｏｌ）得た。

実施例　6

Ｌ－バリンヒドラジド０．２９ｇ（２．２ｍｍｏｌ）をメタノール３ｍｌに溶解した液にラセミ体のＩＰＭＡ０．５ｇ（２．２ｍｍｏｌ）を加えた。　この液にイソプロパノール５ｍｌを加え晶析し、５℃でさらに２時間撹拌した結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再び結晶を濾過して乾燥し、光学純度８０％ｅｅの（Ｒ）－ＩＰＭＡを０．１８ｇ（０．８ｍｍｏｌ）得た。

実施例　9

Ｌ－ロイシンヒドラジド２．４ｇ（１７ｍｍｏｌ）をメタノール１０ｍｌに溶解した液にラセミ体の４－ヒドロキシマンデル酸３．７ｇ（２０ｍｍｏｌ）を加えた。　この液にエタノール１０ｍｌを加え、５℃でさらに２時間撹拌し晶析した。結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再び結晶を濾過して乾燥し、光学純度６５％ｅｅの（Ｒ）－４－ヒドロキシマンデル酸を１．６ｇ（８．６ｍｍｏｌ）得た。

実施例　10

Ｌ－ロイシンヒドラジド４．１ｇ（２８ｍｍｏｌ）をメタノール３０ｍｌに溶解した液にラセミ体の４－クロロマンデル酸４．１ｇ（２０ｍｍｏｌ）を加えた。　５℃で２時間撹拌し晶析した。　結晶を濾過し、その結晶を水中に懸濁させ撹拌しつつ硫酸を加えｐＨ２とした。　再び結晶を濾過して乾燥し、光学純度７０％ｅｅの（Ｒ）－４－クロロマンデル酸を２．１ｇ（１０ｍｍｏｌ）得た。

〔発明の効果〕

以上から明らかなように、本発明によればマンデル酸誘導体を簡便に光学分割できるので、本発明はきわめて有用である。

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